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09/708,276	11/07/2000	Gary J. Nabel	1708642/94	1399

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EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No. 09/708,276	Applicant(s) Nabel
	Examiner William Sandals	Art Unit 1636

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 26, 2003*

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-34 and 36-42* is/are pending in the application.

4a) Of the above, claim(s) *2-28* is/are withdrawn from consideratio

5) ☐ Claim(s) ______ is/are allowed.

6) ☒ Claim(s) *29-34 and 36-42* is/are rejected.

7) ☐ Claim(s) ______ is/are objected to.

8) ☐ Claims ______ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on ______ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on ______ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ______
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s)

DETAILED ACTION

Status of the Claims

1. Claims 2-34 and 36-42 are pending. Claims 2-28 are withdrawn from examination, and are drawn to non-elected inventions I-V. Claim 29 has been amended in Paper No. 13, filed February 26, 2003.

2. The rejection of claims 29 and 32-34 under 35 U.S.C. 102(e) as being anticipated by US 5,672,508 (Gyuris et al.) has been overcome by amendment in Paper No. 13, and the rejection is withdrawn.

3. The rejection of claims 29-34 and 36-42 under 35 U.S.C. 103(a) as being unpatentable over US 5,672,508 (Gyuris et al.) in view of US 5,328,470 (Nabel et al. (B), of record), and further in view of US 5,962,424 (Hallahan et al.) has been overcome by amendment in Paper No. 13, and the rejection is withdrawn.

4. Arguments presented in Paper No. 13 regarding the rejections of the claims under 35 USC 102 and 103 are moot since the rejections have been withdrawn.

5. Claims 29-34 and 36-42 stand rejected under Obvious-type Double Patenting.

6. Claims 29-34 and 36-42 stand rejected under 35 U.S.C. 112, first paragraph.

7. Claims 32, 33 and 36 stand rejected under 35 U.S.C. 112, second paragraph.

8. Claims 29-34 and 36-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/25507 (Seth et al.) in view of US 5,863,904 (Nabel et al., (A)), further in view of US 5,328,470 (Nabel et al. (B), of record), and further in view of US 6,541,197 B2 (Link, Jr. et al.).

Priority

9. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

The transmittal letter sent with the instant application indicates at box 10 that the file is a continuation of Application No. 08/897,333, but box 10 is not checked to indicate the desired action. As a result, the status of the instant application is in question, and requires clarification.

10. Box 7 of the transmittal letter is also not checked, but information provided in box 7 indicates that it is desired to cancel claims 2-16. Since the box has not been checked, the claims have not been cancelled. If it is Applicant's intention to cancel claims 2-16, then a clarification is required.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 29-34 and 36-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 32-35 of U.S. Patent No. 6,177,272. Although the conflicting claims are not identical, they are not patentably distinct from each other because independent claim 29 of the instant application is drawn to a kit (composition) comprising a catheter and a p27 gene. Dependent claims 36-42 recite that the composition includes a gene encoding a cytotoxic agent. Dependent claim 40 recites that the p27

gene and the gene encoding the cytotoxic agent are operative linked such that they form a fusion protein. Claims 32-35 of US Patent No. 6,177,272 are drawn to a composition comprising a polynucleotide encoding a fusion protein comprising p27 and a cytotoxic agent.

While the language is different, the polynucleotide of US Patent No. 6,177,272 and the instant claimed gene are describing the same entities. Further, since the claims contain the "comprising" clause, they are therefore drawn to overlapping subject matter, one making the other obvious.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 29-34 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a "gene encoding a single cyclin-dependent kinase" which is p27. The instant claims and specification provide description only for a species of cDNA which encodes only the transcribed region of the p27 protein. A gene is a genus which comprises non-transcribed control regions both 5' and 3' to the transcribed region. The instant specification does not disclose the relevant identifying characteristics, ie, the

biological, physical and biochemical properties sufficient to describe the claimed invention in such full, clear concise and exact terms which would lead the one of skill in the art to the conclusion that the applicant was in possession of the claimed genus of the p27 gene.

15. Claims 29-34 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims 29-34 and 36-42 are drawn to a kit. No support is provided in the original claims or specification for the word "kit". A kit is a narrower construction of a composition, and since there is no support, either literal or inferential for a "kit", the word "kit" introduces a new concept. Secondly, the specification does not recite compositions that include catheters, so "kit" claims cannot do not derive support from the recitations involving catheters, such as are found at example 2 which do not describe "kits".

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 32, 33 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Claim 32 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Amending the claim to recite that the gene is comprised in an expression vector would cure this deficiency.

19. Claim 33 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Amending the claim to recite that the gene is comprised in a viral vector would cure this deficiency.

20. Claim 36 recites the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Amending the claim to recite that the composition further comprises a gene encoding a cytotoxic agent would cure this deficiency.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 29, 31-34 and 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/25507 (Seth et al.) in view of US 5,863,904 (Nabel et al., (A)).

The claims are drawn to a kit (a composition) for treating proliferative disease in a patient. The kit comprises a catheter and a gene encoding a single cyclin dependent kinase, p27

as recited in claim 29. The catheter may be a double balloon catheter as recited in claim 31. The gene may be in an expression vector, or in a viral particle, and may further comprise a liposome as recited in claims 32-34. The composition may further comprise a second gene encoding a cytotoxic agent which may be cytosine deaminase, thymidine kinase or nitric oxide synthetase as recited in claims 36-38. The gene encoding p27 and the second gene may be operatively linked, which may be a fusion gene as recited in claims 39-41.

Seth et al. teach a gene encoding p27 in a pharmaceutical composition for treating proliferative diseases at page 9 and page 21. The gene may administered intravenously, see page 23, lines 8-12. The gene may be comprised in a viral particle which may be comprised in a liposome, see page 29, lines 21-33. Seth et al. teach the use of a cytosine deaminase gene or HSVTK (thymidine kinase gene) or the No-synthetase gene (nitric oxide synthetase gene) in the alternative to the p27 gene for treating proliferative diseases at, for instance, pages 9 and 21. Seth et al. teach that pWAF1/Cip1 (also known as p21) is also used in the alternative to p27 for the treatment of proliferative diseases.

Seth et al. do not teach that the p27 gene may be administered with a catheter, nor the combination of a p27 gene with a cytotoxic gene in a single nucleic acid construct.

Nabel et al., (A) teach at the summary, the use of the cyclin dependent kinase p21 gene to treat proliferative disease. Nabel et al., (A) teach the composition of a p21 gene comprised in a viral particle expression vector which is comprised in a liposome at column 4, lines 6-30. Nabel et al. teach a p21 fusion gene operatively linked to a cytosine deaminase or thymidine kinase

gene at column 3, line 53 to column 4, line 5. Nabel et al., (A) teach the introduction of p21 into vasculature with a double-balloon catheter at example 1.

One of ordinary skill in the art would have been motivated at the time the instant invention was made to modify the composition of a cyclin dependent kinase, p27 gene, used for treating proliferative diseases comprised in a viral vector, comprised in a liposome as taught by Seth et al. with the composition comprising a cyclin dependent kinase, used for treating proliferative diseases to include the operatively linked cytotoxic gene in a viral vector in a liposome composition delivered to vasculature with a double-balloon catheter of Nabel et al., (A) for the expected benefit of improving the treatment of the proliferative disease by the control of proliferation by the combined activity of the cytotoxic gene with the p27 gene, and improving the method of delivery of the cyclin dependent kinase to the vasculature with a double balloon catheter. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Seth et al. and Nabel et al., (A) who demonstrate a composition comprising a cyclin dependent kinase used for treatment of proliferative disease.

23. Claims 29-34 and 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seth et al. and Nabel et al., (A) as applied to claims 29, 31-34 and 36-41 above, and further in view of US 5,328,470 (Nabel et al. (B), of record).

The claims are drawn to the invention described above, and where the balloon catheter is a single-balloon catheter as recited in claim 30.

Seth et al. and Nabel et al., (A) teach the invention as described above.

Seth et al. and Nabel et al., (A) do not teach a single-balloon catheter.

Nabel et al. (B) teach a double-balloon catheter and a single-balloon catheter which are taught in the alternative as useful in a method of introduction of therapeutic recombinant genes to a vasculature at column 3 to column 5, line 8.

One of ordinary skill in the art would have been motivated at the time the instant invention was made to substitute the double balloon-catheter in the composition of a cyclin dependent kinase, p27 gene, used for treating proliferative diseases as taught by Seth et al. with the single balloon catheter of Nabel et al. (B) because Nabel et al. (B) teach that the single-balloon catheter and double-balloon catheter are used interchangeably. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Seth et al., Nabel et al., (A) and (Nabel et al. (B) who demonstrate a composition comprising a balloon catheter and a cyclin dependent kinase for treatment of proliferative disease.

24. Claims 29-34 and 36-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seth et al., Nabel et al., (A) and (Nabel et al. (B) as applied to claims 29-34 and 36-41 above, and further in view of US 6,541,197 B2 (Link, Jr. et al.).

The claims are drawn to the invention described above, and where the p27 gene and the gene encoding a cytotoxic agent form a dicistronic construct as recited claim 42.

Seth et al., Nabel et al., (A) and (Nabel et al. (B) teach the invention as described above.

Seth et al., Nabel et al., (A) and (Nabel et al. (B) do not teach that the p27 gene and the gene encoding a cytotoxic agent form a dicistronic construct.

Link, Jr. et al. teach at column 7, lines 50-57 that a dicistronic construct formed in retroviral vectors produce higher virus titers, permit the insertion of larger genes and show more stable expression.

One of ordinary skill in the art would have been motivated at the time the instant invention was made to modify the composition of a cyclin dependent kinase, p27 gene, used for treating proliferative diseases comprised in a viral vector, comprised with a second gene encoding a cytotoxic agent as taught by Seth et al. with the dicistronic construct of Link, Jr. et al. for the expected benefit that dicistronic constructs produce higher virus titers, permit the insertion of larger genes and show more stable expression. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Seth et al., Nabel et al., (A), (Nabel et al. (B) and Link Jr. et al. who demonstrate a composition comprising a cyclin dependent kinase in a dicistronic construct and a catheter used for treatment of proliferative disease.

Conclusion

25. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.
Examiner
April 28, 2003

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SUPERVISORY PATENT EXAMINER
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